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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,167	01/08/2002	James Gordon Adamson	6704-268	8982

1059 7590 04/23/2003

BERESKIN AND PARR
SCOTIA PLAZA
40 KING STREET WEST-SUITE 4000 BOX 401
TORONTO, ON M5H 3Y2
CANADA

EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	9

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/926,167	Applicant(s) ADAMSON ET AL.	
	Examiner Brian S Kwon	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *25-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☒ Claim(s) *5,7,15-17,20 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 January 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election of Restriction Requirement Acknowledged

1. Applicants election without traverse the Group A, claims1-24, is acknowledged.

Priority

2. Copies of the certified copies of the priority documents (CANADA 2,266,174 03/18/1999) have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). However, there is no acknowledgment made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) in Declaration.

Drawings

3. The drawings filed January 08, 2002 are objected to by the Draftsperson under 37 CFR 1.84 or 1.152. Applicant is requested to notice the box 5, 10 and 12 made by the Draftsperson. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Objections

4. Claim 7 is objected to because of the following informalities: Typographical error such as "R1" is present in line 9. It appears in view of the instant specification (page 7, line 33 thru page 8, line 1) that R, R4, R5 and R6 refers to "independently selected from H, C1-20 alkyl, X and –(CH2)mX...", not R1 in line 9. Appropriate correction is required.

5. Claims 5, 15-17, 20 and 24 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention .

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The present claim is drawn to a biocompatible chemical composition having oxygen transporting capability and comprising oxygen transporting molecules chemically bound to one or more biocompatible antioxidants selected from e.g., non-enzymatic phenolic compounds, tetrapyrroles, indoles and aminoindoles purine analogs, ascorbic acid, and steroid and alkaloid antioxidants.

(2) The state of the prior art

The hemoglobin crosslinked or conjugated to various agents (e.g., polyaldehyde, hepatocyte modifying substance (e.g., alpha-tocopherol and vitamin C), polyalkyene oxide, nitroxide, hydroxyethylstarch, superoxide dismutase (SOD) catalase, non-antigenic polymer and etc...). However, the art does not teach non-hemoglobin based oxygen carriers (e.g., hemocyanin, hemerythrins, perfluorocarbons) or natural or unnatural mutant hemoglobin species crosslinked or conjugated to biocompatible antioxidants.

(3) The relative skill of those in the art

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art

The unpredictability of hemoglobin conjugates (with cross-linking agents) is very high due to its high specificity.

(5) The breadth of the claims

The claims are very broad. The scope of the claimed oxygen transporting capability composition encompasses non-hemoglobin based oxygen carriers (e.g., hemocyanin, hemerythrins, perfluorocarbons) and natural or unnatural mutant hemoglobin species.

(6) The amount of direction or guidance presented

The guidance given by the specification in regards to non-hemoglobin based oxygen carriers or mutant hemoglobin species crosslinked with biocompatible antioxidants is significantly lacking. The specification does not provide any written description that non-hemoglobin based oxygen carriers or natural or unnatural mutant hemoglobin species would have similarly reacted (chemically) as hemoglobin or hemoglobin derivatives when it is cross-linked or conjugated or intramolecularly bonded. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosrue should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

The specification provides examples of hemoglobin crosslinked with 2,5,7,8-tetramethyl-2-carboxylchroman-6-ol (Trolox) or polyOR-HB-TX conjugates.

(8) The quantity of experimentation necessary

The practitioner must turn to trial and error experimentation to make the instant composition. Therefore, undue experimentation becomes the burden of the practitioner.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 11-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites a chroman carboxylic acid represented by the general formula. However, there is insufficient antecedent basis for this limitation in the specification. Claim 11 is not clear what is meant by R'4-COOH. Claim 11 does not recite any limitation for R'4. Further, it is not clear what is meant by "R1 is a direct bond or C1-8 alkyl chain". Claim 11 does not recite any limitation for R1.

Claim 22 recites the limitation "at least one of R1, R2 and R3 is methyl" in claim 11. There is insufficient antecedent basis for this limitation in the claim.

Claim 23 recites the limitation "R4 is direct bond" in claim 22 which is a dependent claim that depends from claim 11. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The present invention relates to biocompatible chemical composition having oxygen transporting capability and comprising oxygen transporting molecules chemically bound to one or more biocompatible antioxidants selected from e.g., non-enzymatic phenolic compounds, tetrapyrroles, indoles and aminoindoles purine analogs, ascorbic acid, and steroid and alkaloid antioxidants.

8. Claims 1-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Adamson et al. (WO 99/56723).

Adamson discloses a hemoglobin-construct-complex comprising a hemoglobin and a hepatocyte modifying substance such as antioxidant (e.g., alpha-tocopherol and vitamin C) bound thereto, wherein hemoglobin is cross-linked by tetrameric units such as trimesoyl tris (3,5-dibromosalicylate), TTDS (page 9, lines 23-30; page 11, lines 23-31; claim 6 and 16).

9. Claims 1-3, 5-6, 13-15 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Kluger (WO 97/00236).

Kluger teaches a hemoglobin-biomolecule (e.g., hormones) conjugate (claim 18), wherein hemoglobin-biomolecule conjugate is bonded to the crosslinking reagent (e.g., 3,5,3'5'-biphenyltetracarbonyl tetrakis (3,5-dibromosalicylate)). See claims 15-18 and Examples. The represented examples such as norepinephrine or epinephrine falls within the wording of claims 1-3, "non-enzymatic phenolic compounds", "a phenolic compound containing one or more groups of formula"or "a substituted phenolic" (page 12, lines 7-13). Therefore, the reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 4, 7-12, 16-19, 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsia (US 5789376 A) in view of Beach et al. (Archives of Biochemistry and Biophysics, 1992, abstract, 297 (2), 258-64).

Hsia discloses a composition comprising stabilized hemoglobin covalently bound to antioxidant such as a nitroxide, wherein the hemoglobin is cross-linked using polyvalent aldehyde derived from a ring-opened cyclic sugar (e.g., o-raffinose), see claims.

Beach teaches the use of tocopherol analogs (e.g., Trolox) and nitroxides as an antioxidant. The reference teaches that chromanol is the most active antioxidant among other antioxidants.

The teaching of Hsia differs from the claimed invention in the use of other antioxidant, namely 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol (Trolox) in preparing hemoglobin conjugate. To incorporate such teaching into the teaching of Hsia, would have been obvious in

view of Beach who teaches of suggests the use of chromanol based antioxidant such as Trolox as the most active antioxidant. One having ordinary skill in the art would have expected that Trolox would have similar properties as an antioxidant. Further, one having ordinary skill in the art would have been motivated to substitute nitroxide with Trolox having the most active antioxidant property, with the reasonable expectation of success, to provide a hemoglobin composition with enhanced oxygen-transferring function (as blood substitutes) while oxidative stress and oxygen-related toxicity is greatly reduced.

Conclusion

11. No Claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (703)308-5377. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax number for this Group is (703) 308-4556.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brian Kwon

Brian Kwon

ZOHREH FAY

PRIMARY EXAMINER

GROUP 1600